Organic Process Research & Development **2008,** *12,* 946–949

Continuous Organic Synthesis in a Spinning Tube-in-Tube Reactor: TEMPO-Catalyzed Oxidation of Alcohols by Hypochlorite

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Abstract:

Continuous production of aldehydes in high yields (≥90%) can be accomplished by feeding aqueous (sodium hypochlorite/sodium bicarbonate, pH 8.5) and organic (TEMPO/tetrabutylammonium bromide/primary alcohol/toluene or CH_2Cl_2) solutions through the inlets of a spinning tube-in-tube reactor (STT reactor manufactured by Kreido Biofuels [STT is a registered trademark of Kreido Biofuels]) at rotor speeds of 4000−6000 RPM with residence times as short as 1−2 min. This approach eliminates the need for slow addition of the bleach reagent to control this exothermic reaction.

Introduction

The TEMPO-catalyzed oxidation of alcohols to aldehydes and ketones is an important transformation for pharmaceutical synthesis as a result of the selectivity of the reaction between primary and secondary alcohols and the absence of malodorous (Swern oxidation) or hazardous (chromium oxidation) side products.[1–5] An example of the application of this reaction in pharmaceutical chemistry can be seen in the DuPont Merck synthesis of HIV-1 protease inhibitor DMP 323.[1] Perhaps the most useful conditions for this conversion involve the 2,2,6,6-tetramethyl-4-X-1-piperidinyloxy (4-X-TEMPO: X = H, OH, OCH_3, $NHC(=O)CH_3$)-catalyzed oxidation of alcohols by sodium hypochlorite.[1–4] Typical conditions involve the slow addition of sodium hypochlorite buffered with sodium bicarbonate to a biphasic mixture of aqueous sodium or potassium bromide and an organic phase consisting of the alcohol and 4-X-TEMPO (X = H, OCH_3) in toluene, toluene/ethyl acetate, or CH_2Cl_2. Efficient temperature control and rapid mixing (mechanical stirring at or above 1000 RPM) are both necessary to avoid heat build-up resulting from this highly exothermic reaction; slow addition of the hypochlorite is frequently used to control the temperature in this reaction.[1a,3c–f,4] Polymer-bound TEMPO catalysts show comparable or higher reactivity in this oxidation reaction and offer the advantage of facile catalyst recovery.[2c,5]

As a result of the requirement of this reaction for efficient mixing and heat removal, we became interested in examining the potential of running this reaction in a rapid-mixing, continuous-flow reactor, called a spinning tube-in-tube (STT) reactor manufactured by Kreido Biofuels.[6] This research describes the first demonstration of the continuous production of aldehydes in high yields using the TEMPO-catalyzed oxidation of alcohols by hypochlorite in an STT reactor. While this work was being conducted, Friz-Langhals reported that the 4-hydroxy-TEMPO-catalyzed oxidation of two alcohols, 2-butoxyethanol and 2-hydroxyethyl 2-methylpropanoate, by sodium hypochlorite could be performed continuously in a simple 3 mm diameter static mixer tube reactor resulting in the oxidation of β-substituted alcohols to the corresponding aldehydes in yields of 60−77%.[4]

A picture of an STT reactor is shown in Figure 1 and a schematic cross-section of an STT reactor is provided in Figure 2. The basic design of an STT reactor involves the introduction of reactants into the gap (0.25−0.38 mm) between a rapidly rotated (100−12000 RPM) solid or hollow rotor and a stationary outer cylinder (referred to as the "stator"). Heat-exchangers surround the stator and allow for efficient temperature control of the contents of the reactor along the length of the stator. With a rotor−stator gap of 0.25 mm and a rotor working length of 10.1 cm, a Magellan STT reactor has a cavity volume between the rotor and stator of 1.43 mL. Kreido Biofuels also

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(1) (a) Pierce, M. E.; Harris, G. D.; Islam, Q.; Radesca, L. A.; Storace, L.; Waltermire, R. E.; Wat, E.; Jadhav, P. K.; Emmett, G. C. *J. Org. Chem.* **1996**, *61*, 444. (b) Confalone, P. N.; Waltermire, R. E. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K. G., Ed.; Marcell Dekker, Inc.: New York, NY, 1999; pp 205−208.

(2) For a review of this reaction, see: (a) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153. (b) Adam, W.; Saha-Möller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499. (c) Sheldon, R. A.; Arends, I. W. C. E.; Brink, G.-J. TB.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774. (d) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051. (e) Sheldon, R. A.; Arends, I. W. C. E. *J. Mol. Catal. A: Chem.* **2006**, *251*, 200.

(3) (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559. (b) Anelli, P. L.; Banfi, S; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970. (c) Tong, G.; Perich, J. W.; Johns, R. B. *Tetrahedron Lett.* **1990**, *31*, 3759. (d) Siedlecka, R.; Skarżewski, J.; Młochowski, J. *Tetrahedron Lett.* **1990**, *31*, 2177. (e) Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029. (f) Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051. (g) Csuk, R.; Schmuck, K.; Schäfer, R. *Tetrahedron Lett.* **2006**, *47*, 8769.

(4) Fritz-Langhals, E. *Org. Process Res. Dev.* **2005**, *9*, 577.

(5) (a) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **2000**, 271. (b) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Synlett* **2001**, 102. (c) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Special Publ. Royal Soc. Chem.* **2001**, *266*, 118. (d) Burkhardt, O.; Woeltinger, J.; Karau, A.; Philippe, J.-L.; Henniges, H.; Bommarius, A.; Krimmer, H.-P.; Drauz, K. U.S. Patent 6,451,943 B1, 2002. (e) Tanyeli, C.; Gümüş, A. *Tetrahedron Lett.* **2003**, *44*, 1639. (f) Ferreira, P.; Phillips, E.; Rippon, D.; Tsang, S. C.; Hayes, W. *J. Org. Chem.* **2004**, *69*, 6851. (g) Ferreira, P.; Hayes, W.; Phillips, E.; Rippon, D.; Tsang, S. C. *Green Chem.* **2004**, *6*, 310. (h) Pozzi, G.; Cavazzini, M.; Quici, S.; Benaglia, M.; Dell' Anna, G. *Org. Lett.* **2004**, *6*, 441. (i) Gilhespy, M.; Lok, M.; Baucherel, X. *Catal. Today* **2006**, *117*, 114. (j) Michaud, A.; Gingras, G.; Morin, M.; Béland, F.; Ciriminna, R.; Avnir, D.; Pagliaro, M. *Org. Process Res. Dev.* **2007**, *11*, 766.

(6) STT, Magellan, and Innovator are registered trademarks of Kreido Biofuels, formerly Holl Technologies Corporation and Kreido Laboratories. (a) Holl, R.; Gulliver, E.; Hall, N.; Sojka, S. *Innov. Pharm. Technol.* **2003**, *30*, 116. (b) Cihonski, J. *Pristine Processing* **2004**, 25. (c) Holl, R. A.; McGrevy, A. N. U.S. Patent 6,471,392, 2002. (d) Holl, R. A. U.S. Patent 6,752,529, 2004.

10.1021/op800051t CCC: $40.75

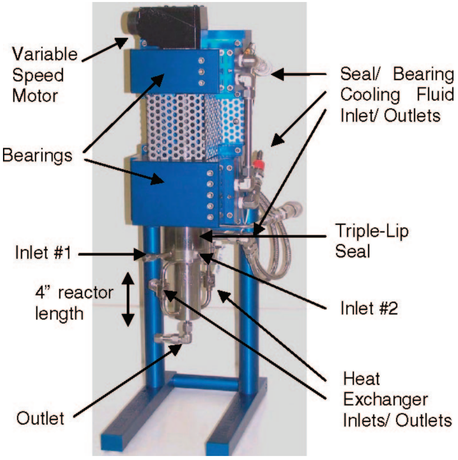


Figure 1. **Picture of a Magellan STT reactor.**

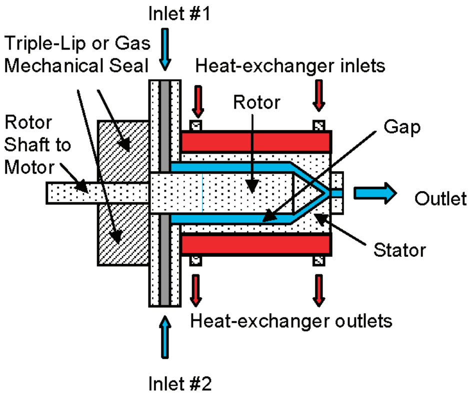
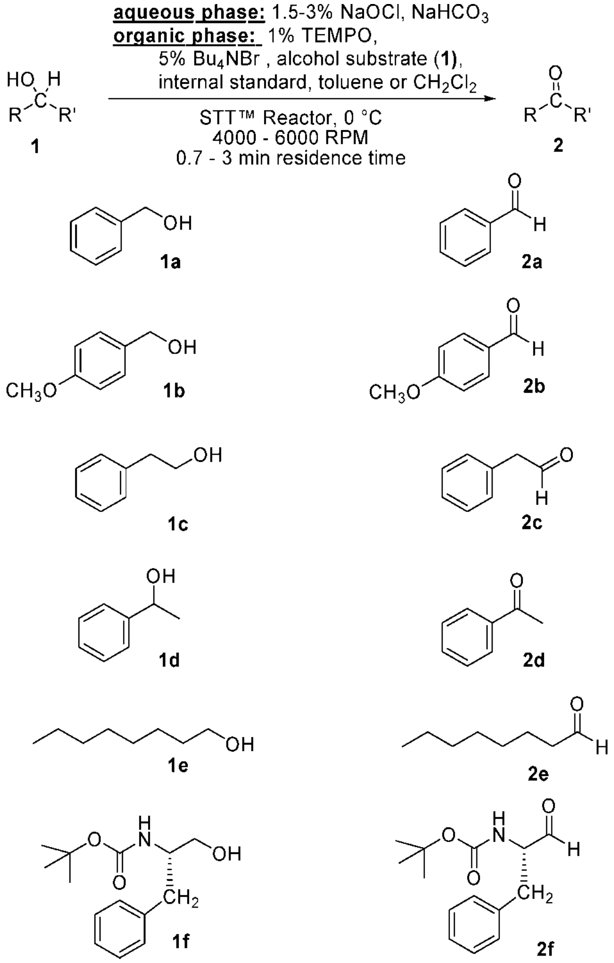


Figure 2. **Cross-section of a Magellan STT reactor.**

Scheme 1. **Reaction conditions for the TEMPO-catalyzed oxidation of alcohols by hypochlorite in an STT reactor**



manufactures the much larger Innovator 200 type STT reactor (reactor volume of 38.6 mL) and the STT 30G. They report that the shear scales from smaller to larger STT reactors.[6]

Results and Discussion

The conditions for the TEMPO-catalyzed oxidation of alcohols by hypochlorite are shown in Scheme 1. Organic (0.2 M alcohol substrate, 2 mM TEMPO, and 10 mM Bu_4NBr in toluene or dichloromethane) and aqueous solutions (3−6% commercial bleach diluted 1:1 with saturated sodium bicarbonate) were introduced through PEEK tubing to the two inlets of a Magellan STT reactor possessing a titanium rotor and stator that were cooled to 0 °C.[7] Syringe or HPLC pumps were used to control the rates of flow of the two solutions into the reactor. Samples were collected as a function of rotor speed and flow rates. The organic phases in these samples were separated from the aqueous phases, dried over anhydrous sodium sulfate, and analyzed by GC/MS. An internal standard was used to quantify the yields of aldehydes and unreacted alcohol substrate in the reaction samples. Isolated yields were obtained by omitting the internal standard and collecting a defined volume of organic phase under a set of reaction conditions.

Table 1 provides aldehyde/ketone yields for the oxidation of alcohols **1a**−**f** by TEMPO/sodium hypochlorite. Essentially quantitative conversion was observed for benzyl alcohol (**1a**), 2-phenylethanol (**1c**), and 1-octanol (**1e**) with short residence times of 86−172 s (0.250−0.500 mL/min flow of the organic and aqueous phases) and at a rotor speed of 4000−6000 RPM.[8] Yields were lower with shorter residence times and with lower rotor speeds (less than 4000 RPM). Longer residence times resulted in somewhat lower yields, possibly due to oxidation of the aldehyde to a carboxylic acid. There was no evidence for the formation of esters under these conditions.[4] Yields were lower at rotor speeds above 6000 RPM or below 4000 RPM and were somewhat greater in toluene compared with CH_2Cl_2. (Table 1, entries 5−8 vs entries 1−4). An orange color of Br_2 was observed in the organic phase in all of these experiments. Diminished yields were obtained when Aliquat 336 (with a chloride counterion) was used in place of Bu_4NBr (Table 1, entry 19). Omission of the quaternary ammonium salt and/or TEMPO catalyst resulted in very low yields (Table 1, entries 20 and 21). The oxidation of benzyl alcohol was examined at a higher concentration of bleach (13%) and in the absence of an organic solvent (Table 1, entry 10). The yield of isolated benzaldehyde was high (91−95%) under these concentrated

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(7) In preliminary experiments, attempts to use a Magellan STT reactor with a stainless steel rotor and stator led to the formation of a thin layer of rust on the surface of the rotor and the yield of aldehyde decreased with time, possibly due to deactivation of the TEMPO catalyst.

(8) The residence time for reactants in the reactor depends on the total flow of reagents and the cavity volume of the reactor, i.e. a total flow of 1 mL/min (0.5 mL/min on each of two inlet flows) yields a residence time of 1.43 minutes for a Magellan reactor with a 1.43 mL volume.

Table 1. **TEMPO-catalyzed oxidation of alcohols in an STT reactor as a function of alcohol structure, temperature, flow rates, and rotor speed.**

entry	substrate[a]	temp (°C)	solvent	flow rate organic (mL/min)	residence time (s)	rotor speed (RPM)	aldehyde/ketone yield[b]
1	**1a**	0	toluene	0.25	172	4000	91−93
2	**1a**	0	toluene	0.25	172	6000	95−96
3	**1a**	0	toluene	0.50	86	4000	90−91
4	**1a**	0	toluene	0.50	86	6000	98−99
5	**1a**	0	DCM	0.25	172	4000	86−90
6	**1a**	0	DCM	0.25	172	6000	81−86
7	**1a**	0	DCM	0.50	86	4000	86−90
8	**1a**	0	DCM	0.50	86	6000	81−86
9	**1a**	0	DCM	1.00	44	6000	89[c]
10	**1a**	0	none	0.50	27	4000	91−95[d]
11	**1b**	0	toluene	0.50	86	4000	90−92[c]
12	**1c**	0	toluene	0.25	172	4000	91−93
13	**1c**	0	toluene	0.25	172	6000	94−96
14	**1c**	0	toluene	0.50	86	4000	90−91
15	**1c**	0	toluene	0.50	86	6000	97−99
16	**1c**	0	toluene	1.00	43	4000	93−94
17	**1c**	0	toluene	1.00	43	6000	92−94
18	**1c**	0	toluene	0.50	86	6000	91[c]
19	**1c**[e]	0	toluene	0.50	86	4000	47−49
20	**1c**[f]	0	toluene	0.50	86	4000	14−22
21	**1c**[g]	0	toluene	0.50	86	4000	11−12
22	**1c**	25	toluene	0.50	86	4000	65−70
23	**1c**	25	toluene	0.50	86	6000	69−70
24	**1d**	0	toluene	0.25	172	4000	75−81
25	**1d**	0	toluene	0.25	172	6000	75−89
26	**1d**	0	toluene	0.50	86	4000	49−56
27	**1d**	0	toluene	0.50	86	6000	71−76
28	**1e**	0	toluene	0.50	86	4000	94−96
29	**1f**	0	toluene	0.50	86	4000	70−82[c]

[a] An organic solution consisting of the alcohol substrate (0.2 M), chlorobenzene or dodecane (0.1 M), Bu$_4$NBr (10 mM), and TEMPO (2 mM) dissolved in the indicated organic solvent, and an aqueous solution consisting of a 1:1 mixture of saturated sodium bicarbonate and 3−6% bleach, were fed through the inlets of a Magellan STT reactor at the indicated temperature, flow rate, and rotor RPM. [b] Unless otherwise noted, yields are based on GC/MS analysis with an internal standard (chlorobenzene or dodecane). [c] Isolated yield after separation and drying of organic phase followed by chromatography on silica gel. [d] Reaction run without an organic solvent using 13% bleach, as described in the Experimental Section. Yields were determined using chlorobenzene as an internal standard. [e] Aliquat 336 (chloride counterion) was used as the phase-transfer agent (5%). [f] Quaternary ammonium salt phase-transfer agent was omitted from this reaction. [g] TEMPO and quaternary ammonium salt phase-transfer agent were omitted from this reaction.

conditions, and there was no increase in the temperature of the reactor output compared to the stator temperature setting (0 °C).

The yield of acetophenone from *sec*-phenethyl alcohol increased with increasing residence time but was still not complete even with a residence time of over 400 s (Table 1, entries 24−27). The slower reactivity of *sec*-phenethyl alcohol is consistent with literature reports of the slower reactivity of secondary alcohols in the TEMPO-catalyzed oxidation reaction.[3]

Aldehydes were isolated in excellent yield from these reactions in the absence of internal standard and after column chromatography. Benzaldehyde (**2a**) could be obtained in 89% isolated yield from benzyl alcohol (**1a**) with a residence time of only 44 s in dichloromethane (Table 1, entry 9). Anisaldehyde (**2b**) could be obtained in 90−92% yield in toluene with a residence time of 86 s (Table 1, entry 11). Phenylacetaldehyde (**2c**) was obtained from 2-phenylethanol (**1c**) in 91% isolated yield with a residence time of 86 s in toluene (Table 1, entry 18). By comparison, a literature report indicated only an 87% yield of phenylacetaldehyde from 2-phenylethanol when sodium hypochlorite was added slowly over 45 min and with stirring for 80 min after complete addition.[3d] Only 3 mmole of phenylacetaldehyde was produced in the 125 min reaction time. This same quantity could be generated using a Magellan STT reactor in less than 2 min. Lower yields (70−82%, unoptimized) were obtained of the BOC-protected aldehyde **2f**; the same aldehyde was prepared in a batch process in 90% yield (Table 1, entry 29).[1b]

Conclusion

These results show that when the TEMPO-catalyzed oxidation of alcohols by hypochlorite is performed in an STT reactor, there is an increased yield of aldehyde product, an increased reaction rate, and an ability to produce aldehyde products continuously. In principle, the scale of this reaction could be increased by running the reaction in an Innovator 200 type STT reactor which has a 25-fold larger reactor volume than the Magellan STT reactor used in this study. Kreido has constructed a much larger reactor for the production of biodiesel. We hypothesize that the rapid mixing of reactants and efficient heat transfer are responsible for the high yield and rapid reaction observed in this research, and we postulate that highly exothermic and mixing-limited (i.e., solid-forming) reactions may be improved using an STT reactor. We are currently examining whether the STT reactor can improve these and other pharmaceutically relevant reactions.

Experimental Section

Reagents were purchased from Fisher Scientific or Sigma-Aldrich and used without additional purification. GC/MS analysis was performed on a Shimadzu QP-5000 equipped with an AOC-20i autosampler. Solutions of the alcohol (0.2 M), TEMPO (2 mM), quaternary ammonium salt (10 mM), and internal standard (chlorobenzene or dodecane 0.1 M) were prepared fresh for each experiment by weighing the appropriate quantity of the component into a volumetric flask and bringing the volume to the mark with the solvent (toluene or CH_2Cl_2) used in the experiment. Bleach solutions were similarly prepared fresh for each experiment by diluting 6% commercial bleach (approximately 0.88 M) with saturated sodium bicarbonate in a volumetric flask. Isolated yields were obtained using similar solutions but without the internal standard.

Solutions were introduced into a Magellan STT reactor using Shimadzu LC10-AT*vp* HPLC pumps or a Harvard Apparatus Pump 22 infusion/withdraw dual syringe pump.[6] In all cases, PEEK tubing was used to connect the pumps to the Magellan STT reactor. When syringe pumps were used, PEEK plastic tubing was connected to a luer lock adapter using HPLC and/or Swagelok fittings. The temperature of the stator and the STT bearings were controlled using Julabo F33 and F12 heater/chillers containing propylene glycol as the coolant. In some experiments, the solutions were precooled using simple heat exchangers (not shown in Figures 1 or 2) which were set to the same temperature as the heat exchangers on the stator; the presence or absence of the heat exchangers did not impact the yield. Whenever the flow rate or rotor speed was changed in an experiment, the reactor was flushed with a total of at least five reactor volumes (7−15 mL) to ensure equilibration of the reactor and its contents.

Mixtures of organic and aqueous phases flowing out of the STT reactor were collected in a small vial and the organic phase was quickly removed and dried over anhydrous sodium sulfate. The filtered solutions were loaded into labeled 2 mL GC/MS sample vials and diluted to approximately 2% of their original concentration. For each set of reactor conditions, a minimum of two samples were collected, and these samples were run in duplicate on the GC/MS. Duplicate runs of each substrate were performed with different reagent solutions. Standard procedures were used to obtain response factors between the authentic distilled aldehyde or ketone product, the alcohol substrate, and chlorobenzene or dodecane (internal standard).

Isolated yields were obtained by collecting the mixture of organic and aqueous phases in a separatory funnel. The contents of the separatory funnel were periodically separated. After approximately 30 mL of product stream was collected, the magnesium sulfate was filtered, and 25 mL of the filtrate was collected in a volumetric flask. After the solvent was removed *in vacuo*, the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as the eluent.

In an attempt to determine whether this reaction could be scaled to higher concentrations of alcohols and bleach, a reaction was run without the use of an organic solvent and using 13% commercial bleach. A mixture of benzyl alcohol (7.2 M), chlorobenzene (1.1 M), TEMPO (0.02 M), and tetrabutylammonium bromide (0.067 M) was used as the organic phase, and commercial 13% sodium hypochlorite (saturated with solid sodium bicarbonate and filtered) was used as the aqueous phase. A flow rate of 2.5 mL/min for the bleach solution and 0.5 mL/min for the organic phase was used in this experiment. The yield of benzaldehyde was determined using an internal standard.

Acknowledgment

We acknowledge the loan of a Magellan STT reactor by Kreido Biofuels and the California State University Program for Education and Research in Biotechnology (CSUPERB) for a grant in support of this research.

Received for review September 22, 2005.

OP800051T